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Original article

Early living donor liver transplantation for alcohol-associated hepatitis

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ABSTRACT

Introduction and Objectives: Lately, there has been a steady increase in early liver transplantation for alcohol-associated hepatitis (AAH). Although several studies have reported favorable outcomes with cadaveric early liver transplantation, the experiences with early living donor liver transplantation (eLDLT) are limited. The primary objective was to assess one-year survival in patients with AAH who underwent eLDLT. The secondary objectives were to describe the donor characteristics, assess the complications following eLDLT, and the rate of alcohol relapse.

Materials and Methods: This single-center retrospective study was conducted at AIG Hospitals, Hyderabad, India, between April 1, 2020, and December 31, 2021.

Results: Twenty-five patients underwent eLDLT. The mean time from abstinence to eLDLT was 92.4 ± 42.94 days. The mean model for end-stage liver disease and discriminant function score at eLDLT were 28.16 ± 2.89 and 104 ± 34.56, respectively. The mean graft-to-recipient weight ratio was 0.85 ± 0.12. Survival was 72% (95%CI, 50.61−88) after a median follow-up of 551 (23-932) days post-LT. Of the 18 women donors,11 were the wives of the recipient. Six of the nine infected recipients died: three of fungal sepsis, two of bacterial sepsis, and one of COVID-19. One patient developed hepatic artery thrombosis and died of early graft dysfunction. Twenty percent had alcohol relapse.

Conclusions: eLDLT is a reasonable treatment option for patients with AAH, with a survival of 72% in our experience. Infections early on post-LT accounted for mortality, and thus a high index of suspicion of infections and vigorous surveillance, in a condition prone to infections, are needed to improve outcomes.

1. Introduction

Corticosteroid therapy for alcohol-associated hepatitis (AAH) is associated with improved short-term survival [1,2]. Corticosteroid therapy can decrease short-term mortality by approximately 40%. The maximum benefit is seen in patients with Model for End-Stage Liver Disease (MELD) scores between 25 and 39, whereas mortality in corticosteroid non-responders is 75% at six months [1,3]. However, there are contraindications for corticosteroid therapy in AAH, including uncontrolled infection, renal failure, and gastrointestinal bleeding. Further, approximately, 35% of patients with AAH do not respond to corticosteroids, and the mortality in such individuals is higher in the absence of early liver transplantation [4,5]. In such situations of contraindications for corticosteroid therapy or corticosteroid nonresponse, early liver transplantation (eLT) has been noted to be lifesaving [5]. In recent years, eLT has increased 5-8-fold in the United States [6]. However, barriers and healthcare burdens unique to eLT for patients with AAH have recently been highlighted [7,8]. Thus, most patients are denied eLT due to

Abbreviations: AAH, alcohol-associated hepatitis; ARLD, alcohol-related liver disease; COVID-19, coronavirus disease 2019; eLT, early liver transplantation; eLDLT, early living donor liver transplantation; HAT, hepatic artery thrombosis; INR, international normalized ratio; mDF, Maddrey's discriminant function; MELD, model for end-stage liver disease; MOF, multi-organ failure

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psychosocial factors rather than medical reasons [7]. Furthermore, prolonged hospital stays and a higher number of outpatient visits impact healthcare and cost burdens. [8,9] These barriers have, however, been better described in the context of deceased donor liver transplantation (DDLT). The barriers and outcomes in South Asian centers, where living donor liver transplantation (LDLT) is predominant, are less known. A study from India has reported excellent outcomes with LDLT in patients with AAH [10]. The study included patients with AAH who underwent LDLT even after six months of abstinence and did not describe donor characteristics unique to LDLT settings [10]. Therefore, we aimed to assess the characteristics of recipients and donors and the outcomes of patients with AAH who underwent eLDLT within six months of abstinence.

2. Materials and Methods

This single-center retrospective study was conducted at AIG Hospitals, Hyderabad, India, between April 1, 2020, and December 31, 2021. The main objective of this study was to assess the one-year survival of patients who underwent eLDLT. The secondary objectives were to describe the donor characteristics in our settings, assess complications following eLDLT, and assess the rate of alcohol relapse.

2.1. Inclusion and exclusion criteria

Patients who underwent eLDLT for AAH were included. These patients had either had contraindications for corticosteroid therapy in the form of sepsis or acute kidney injury (AKI) and underwent eLDLT after adequate treatment of the complications or were corticosteroid non-responders. All patients planned for eLDLT underwent regular counseling and were treated with anti-craving agents (baclofen or naltrexone). In addition, patients scheduled for eLDLT had to get psychiatry clearance before surgery. Patients deemed motivated enough, and with adequate family, support proceeded with eLDLT after clearance by the multi-disciplinary team, including four hepatologists, two psychiatrists, six surgeons, and eight anesthesiologists. The donor was also required to obtain approval from a psychiatrist before donation. We excluded patients who died on the waitlist for LDLT, patients who lacked the motivation to remain abstinent, and those who had relapsed before planned LDLT.

2.2. Definitions

AAH: Patients satisfying the National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria were diagnosed as AAH [11]. Accordingly, AAH was defined as the onset of jaundice (serum bilirubin >3 mg/dl) within two months of the last significant alcohol use, with aspartate aminotransferase (AST) >50 U/L and <400 U/L, AST/alanine aminotransferase (ALT) ratio >1.5, and exclusion of other causes of liver disease in a patient with daily harmful alcohol use for ≥6 months. All patients had documented negative viral hepatitis markers, including hepatitis A (IgM antibody), hepatitis B (surface antigen), hepatitis C (antibody), hepatitis E (IgM antibody), dengue (IgM antibody), Epstein-Barr virus (IgM antibody), cytomegalovirus (DNA), and herpes simplex virus (RNA). Additionally, autoimmune markers, including anti-nuclear and anti-mitochondrial antibodies, were confirmed to be negative and with normal serum total immunoglobulin G (IgG) levels. Biopsy was performed in select cases when the diagnosis of AAH was unclear, and the patient was deemed fit enough to tolerate the invasive procedure [12]. eLDLT was defined as a patient undergoing liver transplantation within six months of the last alcohol intake [5]. A Lille score of >0.45 on day seven was considered a non-response to corticosteroids. Any amount of alcohol intake post-transplant was considered a relapse. Relapse was classified according to the latest suggestion by Arab and Izzy *et al.* as mild relapse (occasional slips ≤ once per month); moderate relapse (≤ 14 drinks/week for men and ≤ 7 /week for women); and severe relapse (regular use above recommended standards of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) or with associated morbidity or mortality, which includes alcohol-related pancreatitis, acute alcohol-associated hepatitis, graft loss or other medical problems directly associated with return to drinking) [13].

2.3. Center

A full-fledged in-house LT program began in 2020 in our hospital. Transplantation services continued through the pandemic, and an average of 75 living donor liver transplants are performed each year.

2.4. Statistical analysis

Statistical analyses were performed using SPSS ver.25 (IBM corp. New York, USA). Continuous variables are expressed as mean (standard deviation [S.D.]) or median (range) for parametric data. Categorical variables are expressed as n (%).

2.5. Ethical statement

An informed consent form was obtained from each patient (or a responsible guardian) included in the study, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institutional Ethics committee of AIG (letter no. AIG/IEC-Post BH&R 57/01.2022-01).

3. Results

Thirty-four patients with AAH as the first decompensating event were assessed for inclusion. Nine patients were excluded: seven patients who were scheduled for eLDLT died of sepsis on the waitlist (three of them had received corticosteroids and were non-responders), and two patients were deemed unfit for LDLT due to poor motivation (including one patient who had relapsed before LDLT). A total of 25 patients underwent eLDLT. Three patients in the eLDLT group had biopsy-proven AAH, while the rest were diagnosed based on clinical presentation and laboratory data. The explants of all patients who underwent eLDLT had features of AAH, with cirrhosis documented in 76% of the patients (n=19). All the patients were men, and their mean age was 40.72 ± 8.37 years. Approximately 76% of patients had ascites. Seventy-two percent, 56%,44%, and 24% of patients had acute kidney injury (AKI), hepatic encephalopathy, sepsis, and a history of acute variceal bleeding before eLDLT. The peak serum creatinine in patients with AKI was 2.52 ± 0.55 mg/dl. Eight of the eighteen patients with AKI received terlipressin for hepatorenal syndrome-AKI. All eight patients responded to terlipressin. The rest of the sepsis-related AKI patients (n=10) recovered with volume expansion and sepsis control. The mean MELD and Discriminant function (mDF) score at the time of transplantation was 28.16 ± 2.9 and 104 ± 34.56, respectively. The biochemical variables and severity scores are presented in Table 1. The mean time from abstinence to eLDLT was 92.4 ± 42.94 days. The mean graft-to-recipient weight ratio (GRWR) was 0.85 ± 0.12. Thirty-two percent (8/25) of individuals had GRWR between 0.6 and 0.8 and the rest had GRWR above 0.8.

3.1. Survival analysis

Survival in those who underwent eLDLT was 72% (18/25; 95%CI, 50.61-88) over a median follow-up duration of 551 (23–932) days.

3.2. Donor characteristics

Twenty-eight individuals willing to donate were evaluated. Three individuals underwent liver biopsy in view of higher liver attenuation

Table 1
Baseline characteristics of patients

Variables	eLDLT group (n = 25)
Age (Years)	40.72 ± 8.37
Males (n,%)	25 (100%)
Ascites (n, %)	19 (76%)
Tobacco use (n, %)	18 (72%)
Chewers	12
Smoker	3
Chewer + smoker	3
Acute kidney injury (n, %)	18 (72%)
Acute variceal bleed (n, %)	6 (24%)
Hepatic encephalopathy (n, %)	14 (56%)
Sepsis (n, %)	11 (44%)
Hemoglobin (g/dL)	9.2 ± 2.05
TLC (cells/L)	13, 464 ± 6882.4
Platelets (x 10^9/l)	123.84 ± 38.73
Serum creatinine (mg/dl)	0.95 ± 0.31
PT (seconds)	32.2 ± 8.35
INR	2.7 ± 0.71
Serum sodium (me/dl)	131.36 ± 4.18
Total bilirubin (mg/dl)	17.91 ± 7.23
Direct bilirubin(mg/dl)	9.17 ± 4.42
Total protein (g/dL)	6.04 ± 1
Serum albumin (g/dL)	2.81 ± 0.36
mDF at diagnosis	107.08 ± 35.94
mDF at LT	104.1 ± 34.56
MELD at diagnosis	29.68 ± 4.68
MELD at LT	28.16 ± 2.89

eLDLT, early living-donor liver transplantation; LT, liver transplantation; TLC, total leukocyte count; PT, prothrombin time; INR, international normalized ratio; mDF, modified Maddreys discriminant function score; MELD, model for end-stage liver disease.

index (LAI) and body mass index (BMI). Of them, one had F2 fibrosis and was declined. The other two individuals (with significant steatosis on non-invasive methods) underwent liver biopsy after weight loss and were taken up for donation as the biopsy showed mild steatosis. Another female was declined due to a low GRWR of 0.56. The third donor was diagnosed with peritoneal tuberculosis on evaluation for liver donation and was declined. She complained of vague abdominal pain and loss of appetite for the previous three months. The age and BMI of accepted donors were 35.72 ± 10.44 years and 24.91 ± 3.62 kg/m^2, respectively. The mean LAI and proton density fat fraction of accepted donors was 9.54 ± 5.53 and 4.58% ± 3.05%, respectively. Seventy-two percent of the donors were women (n=18), and the rest were men. The donor was often a wife (n=11) of the recipient (Table 2). The median duration from marriage to liver donation was 9 (0.3–22) years. Fifty-five percent had two children, 18% had one child, 9% had three children, and 18% did not have children at the time of donation.

3.3. Complications following eLDLT

Seven patients died within one year (Table 3). The mean GRWR among those who died (0.81 ± 0.14) and were alive (0.86 ± 0.11) was comparable (P=0.36). Three patients died of fungal sepsis (two were corticosteroid non-responders before LT). All three patients had positive galactomannan tests, with one having florid bilateral cavitary lung lesions. Aspergillus fumigatus growth was noted in the bronchoscopic alveolar lavage of the cavitary lesion. Two patients (one was a corticosteroid non-responder before LT) died of bacterial sepsis and multi-organ failure (MOF). One patient developed hepatic artery thrombosis (on day 9), leading to early graft dysfunction and death on day 23. Thrombolysis was attempted twice but failed. One patient developed a bile leak from the cut surface, which was managed with endoscopic stenting, and recovered. However, the patient died of severe coronavirus disease 2019 (COVID-19) on day 160. Three other recipients developed infections that resolved with antibiotic therapy: urosepsis (*E. coli*), pneumonia (*Klebsiella pneumoniae)*, and bacteremia (*Klebsiella pneumoniae*).

Renal recovery: Of the eighteen patients with pre-transplant AKI, three (two with prior HRS-AKI and one with sepsis-AKI) developed AKI post-transplantation. One patient with HRS-AKI developed chronic kidney disease five months after eLDLT. The other two died of MOF.

Table 2
Donor relationship to the recipient

Relation to recipient	n
Wife	11
Mother	2
Mother-in-law	2
Sister	2
Son	2
Nephew	2
Daughter	1
Father	1
Brother	1
Brother-in-law	1

3.4. Alcohol relapse

Twenty percent (5/25) of the patients relapsed. The time to relapse was 87 (32–712) days. Three patients had a mild relapse (slips), and two had a severe relapse. One patient with severe relapse developed biopsy-proven AAH post-transplantation on day 218 and was treated with corticosteroid therapy. He was started on baclofen; however, he again had a moderate relapse and was admitted to a de-addiction center. Another patient with severe relapse developed progressive graft failure due to non-compliance with medications due to financial instability, continued alcohol misuse (severe relapse) due to depression, and died from bacterial sepsis. The other three patients (mild relapse) have stable graft function.

4. Discussion

Alcohol-associated hepatitis (AAH) is associated with high mortality, and the treatment modalities evaluated include pentoxifylline and corticosteroids. Pentoxifylline has not been associated with survival benefits and thus has no proven therapeutic benefit [14]. Conversely, corticosteroid therapy in patients with AAH is associated with short-term mortality benefits [1]. However, not all patients are suitable for such therapy because of concerns about sepsis, renal injury, or gastrointestinal bleeding. Furthermore, non-responders to corticosteroids have higher mortality rates [5]. Therefore, several interventions, including granulocyte colony-stimulating factor (G-CSF), fecal microbiota transplantation, IL-1 receptor antagonist, and anti-TNF therapy, have been evaluated, but they have not been successful in providing a benefit [15–18].

Liver transplantation remains a viable option for patients with severe AAH who are not candidates for corticosteroid therapy or are non-responders. Several studies have evaluated the role of cadaveric LT in AAH [5,19–22]. However, in India, due to organ shortage and increased access to living donors, LDLT has been a feasible option, but its benefit and role in AAH have not been well reported. Recently, there has been a significant increase in alcohol consumption in South Asian countries, especially India and China [23]. In addition, there has been a substantial increase in harmful alcohol consumption during the COVID-19 pandemic [24,25]. The burden of ARLD is expected to increase further, as is the number of eLDLTs for AAH. Therefore, knowledge of LT strategies for AAH, particularly eLDLT, required further study. Thus, we set out to describe our experience and unique challenges with eLDLT.

The initial study by Choudhary *et al.* reported 84% survival in one year. However, the study included fewer sick patients. The mean

Table 3
Characteristics of the patients who died after eLDLT.

Case number	Age of recipients (years)	Age of donor (years)	Relation	GRWR	Time from last alcohol intake to eLDLT (Days)	Time from last steroid intake to LT	MELD/mDF at eLDLT	Day of mortality after eLDLT	Cause of mortality
1	37	31	Wife	0.68	60	-	33/160.4	56	Sepsis - Fungal pneumonia
2	43	33	Wife	0.81	32	21	28/93.5	40	Fungal sepsis (cavity in lung)
3	55	29	Nephew	0.94	68	32	30/105.2	53	Wound infection, Fungal sepsis, AKI
4	38	32	Sister	0.97	55	-	33/183.2	23	HAT, Biliomas, early graft dysfunction
5	39	35	Wife	0.75	42	17	27/81	64	Bacterial sepsis with MOF.
6	42	34	Wife	0.6	90	-	30/158	97	Septic shock with MOF. Non-compliance to medications. Alcohol relapse.
7	41	34	Wife	0.95	110	-	33/158.8	160	COVID-19

eLDLT, early living donor liver transplantation; MELD, model for end-stage liver disease; mDF, modified Discriminant Function score; HAT, hepatic artery thrombosis; MOF, multi organ failure; COVID-19, coronavirus disease.

MELD and mDF scores were 22 and 53 which were much lower compared to 28 and 104 in our cohort. Furthermore, the mean time from abstinence to transplantation was three months in our cohort compared to four months in the previous study. Moreover, Choudhary *et al*. included some patients being transplanted after six months of abstinence. The mean GRWR was 0.85 ± 0.12 in our cohort compared to 0.95 ± 0.17 in the previous study. These may be the possible reasons for the lower survival of 72% in our cohort.

A recent study by Weinberg *et al*. described the survival after LT among those with prior decompensating events with the first event as AAH [26]. Survival at one year was 93% in those with AAH as the first event vs. 86% in those with prior history of decompensation. The authors reported that prior history of decompensation was associated with a high risk of post-LT mortality and alcohol relapse [26]. However, despite AAH being the first decompensating event in our study, eLDLT was associated with lower survival. This lower survival in contrast to previous reports on cadaveric LT can be due to multiple reasons, including a higher pre-operative MELD, AKI, higher incidence of infections (pre- and post-LT), and higher alcohol relapse [27–29]. Several studies have reported that the long-term survival of patients with AAH is 30% and is dependent on the presence of cirrhosis and alcohol relapse [5,30–32]. Therefore, LT is a viable option with long-term survival benefits in a select group of motivated patients with AAH and our experience presents an opportunity to improve further.

Infections are common in AAH patients [33–35]. Most common cause of mortality was sepsis during the waiting period and after eLDLT. Fungal infections in the post-transplant period frequently complicate the outcomes of patients with AAH. Choudhary *et al*. reported infections in approximately 70% of patients with AAH post-LT, with more than 20% developing fungal infections [10]. Forty-four percent of patients had infections prior to LT. Pre-LT infection increases the risk of post-LT infection and mortality [36,37]. It is well known that the incidence of MDR infections is high in India [38,39]. Thus, regular screening with serological and conventional culture methods in these high-risk populations may aid in early identification and intervention and improve outcomes. Furthermore, lower immunosuppression strategies may also help in reducing the incidence of infection in areas with a high burden of infection. We have modified our protocol and performed procalcitonin levels frequently and surveillance cultures every 7 days and incorporated a lower immunosuppression regimen for sick patients undergoing LT. Further, we will explore if higher GRWR might be of benefit in this population of AAH that has an impaired immune function and is susceptible to infections.

Stronger family support and regular counseling may benefit LT recipients. The mean time from the last intake of alcohol to LT was three months. The reason for this delay (apart from the time taken for stabilization) is the lack of acceptance of LT upfront and the need for careful assessment of LT, including regular counseling of the patient and attendants. Despite adequate measures ensured for candidate selection, 20% relapsed post-LT. Previous studies have reported alcohol relapse among 10–20% of recipients [5,21,40]. Furthermore, a high alcohol intake is more frequent in patients who undergo early LT [22]. Early alcohol relapse after transplantation is known to predict poorer long-term survival post-LT [41]. Regular counseling and deaddiction measures are required post-LT to prevent alcohol relapse.

Of interest was the observation that all the recipients were men, and the donors were women, highlighting the cultural issues in India. Most often, these men belong to the productive class and are the sole financial source for the family. As such, the possible overt or covert societal pressures may be factors in these observations and needs an effort in cultural and societal modifications. Furthermore, donor-recipient gender mismatch is known to increase the risk of graft failure, which may be one of the reasons for poorer survival in this cohort of patients [42].

The main limitation of this study was its retrospective analysis from a single center. In addition, the study may have been prone to selection bias considering only sick patients deemed unfit for medical therapy or were non-responders to corticosteroid therapy being offered eLDLT. Lastly, we did not assess biomarkers or clinical and psychosocial predictors of alcohol relapse, which are essential for the better selection of transplant candidates and preservation of graft function. However, a key strength of this study is that it highlights the unique features of eLDLT for AAH in India, suggesting eLDLT as a reasonable option for motivated patients with AAH who are corticosteroid ineligible and/or non-responder to corticosteroid therapy. Cadaveric transplants are less frequent in India, and the lack of public health care policies, transplant registries, and funding to support LT limits the accessibility to LT [43]. More importantly, with the increasing prevalence of AAH worldwide, shortage of organs, and lack of standard therapy for AAH, policies to curb alcohol misuse are required [44].

5. Conclusions

eLDLT is a reasonable option for patients with AAH. Our survival rate was 72% over a median follow-up duration of 551 (23–932) days. Strategies to prevent early mortality due to infections are needed in regions with a high incidence of infections.

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Declaration of Competing Interests

None.

CRediT authorship contribution statement

Anand V. Kulkarni: Conceptualization, Data curation, Writing – original draft. **Raghuram Reddy:** Data curation, Writing – original draft, Supervision. **Juan Pablo Arab:** Writing – review & editing. **Mithun Sharma:** Writing – original draft. **Sameer Shaik:** Data curation. **Sowmya Iyengar:** Writing – original draft. **Naveen Kumar:** Project administration. **Naveen Sabreena:** Project administration. **Rajesh Gupta:** Writing – review & editing. **Giri Vishwanathan Premkumar:** Supervision. **Balachandran Palat Menon:** Supervision. **Duvvur Nageshwar Reddy:** Writing – review & editing. **Padaki Nagaraja Rao:** Conceptualization, Writing – review & editing. **K. Rajender Reddy:** Writing – review & editing.

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